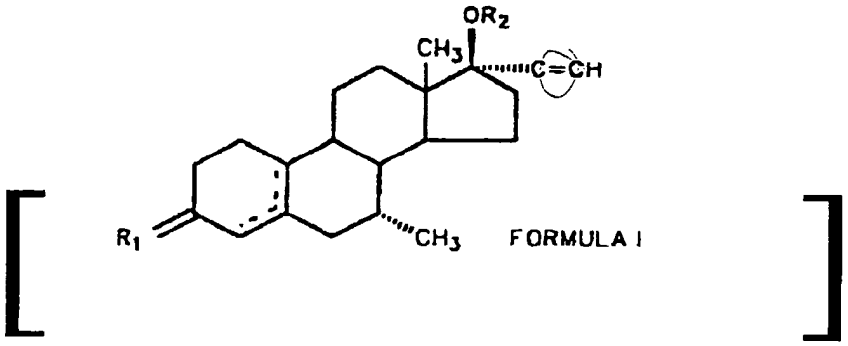
4. The method according to claim 1, wherein the a 7α-methyl-17α-ethynyl-estrane derivative is 7α-methyl-17α-ethynyl-17β-hydroxy-estra-5(10)-en-3-one.

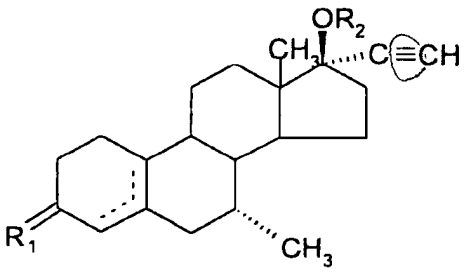
6. The method of Claim 5 wherein the mammal is a human.

II. In the Claims (Marked Version)

1. A method of inhibiting the atherosclerotic process, comprising administering to a mammal an effective amount of a 7α-methyl-17α-ethynyl-estrane derivative having the general formula I



FORMULA I



Formula I

wherein

R_1 = H(OR_3) or O;

R_2 = H or (C_{1-18})Acyl;

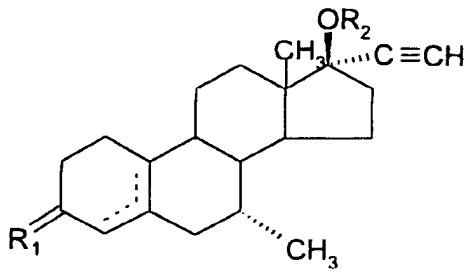
R_3 = H or (C_{1-18})Acyl;

and the dotted line represents a double bond in the 4, 5- or the 5, 10-position.

III. In the Specification (Clean Sheet)

(Page 4, lines3)

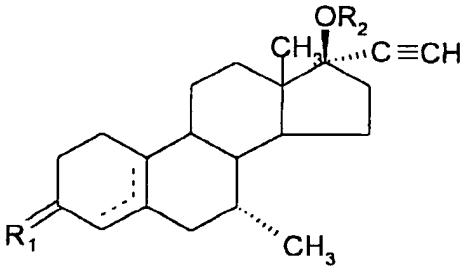
B2



Formula I

(Page 21, Figure in the Abstract)

B3



IV. In the Specification (Marked Version)

Please cancel the figure on page 4, line 3 and replace with

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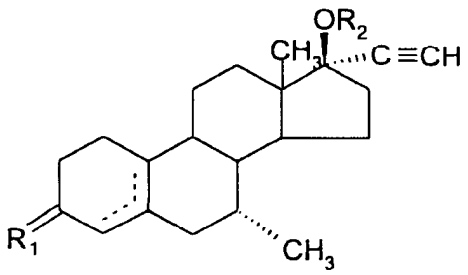

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Please cancel the Figure in the Abstract and replace with

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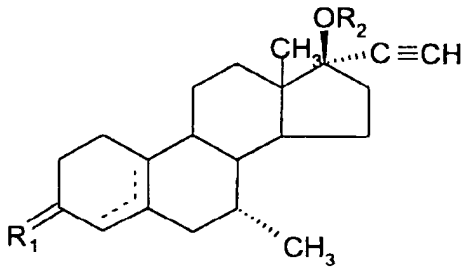

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V. Remarks

A. Typographical Corrections

Applicants have amended Claim 1; page 4, line 3; and, the Abstract to correct a typographical error in a figure. The figures in Claim 1, in the

Abstract and on page 4, line 3 show a double bond at the group at position 17. However, the specification clearly states that this group has a triple bond.

For example, the error is obvious from the name of the compounds: "7α–methyl-17 α-**ethynyl**-estrane derivative". In addition, the examples mention, throughout the specification, the steroid 7α–methyl-17 α-**ethynyl**-17β-hydroxy-estra-5(10)-en-3-onc (Org OD-14; Tibolone). Moreover this compound is known in the literature and its structure established. Accordingly, Applicants respectfully request entry of the amendments. No estoppel should result as the correction is merely typographical in nature.

B. Rejection Under 35 USC §103(a)

The Examiner has rejected the pending claims under 35 USC § 103 (a) over Haenggi et al. in view of Berglund. Applicants respectfully request reconsideration of the rejection in light of the analysis of the four factors concerning obviousness as announced by the Supreme Court.

It has long been the law that an obviousness determination requires analysis of (1) scope and content of prior art; (2) the differences between the prior art and the claims at issue; (3) the level of ordinary skill in the art; and, (4) objective evidence of non-obviousness. Stated another way, "[o]bviousness is a question of law based on findings of underlying facts relating to the prior art, the skill of the artisan, and objective considerations." ***See Graham v. John Deere Co.***, 383 U.S. 1, 17, 148 USPQ 459, 467 (1966). As well, as in the present case, to establish a prima facie case of

obviousness based on a combination of the content of various references, there must be some teaching, suggestion or motivation in the prior art to make the specific combination that was made by the applicant. ***In re Raynes*** , 7 F.3d 1037, 1039, 28 USPQ2d 1630, 1631 (Fed. Cir. 1993); ***In re Oetiker*** , 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1445 (Fed. Cir. 1992). Therefore, it is axiomatic that obviousness can not be established by hindsight combination to produce the claimed invention. ***In re Gorman*** , 933 F.2d 982, 986, 18 USPQ2d 1885, 1888 (Fed. Cir. 1991). As was discussed in ***Interconnect Planning Corp. v. Feil***, 774 F.2d 1132, 1143, 227 USPQ 543, 551 (Fed. Cir. 1985), it is the prior art itself, and not the applicant's achievement, that must establish the obviousness of the combination. Here, as will be illustrated, Applicants invention is not rendered obvious by the prior art.

The Examiner contends that Haenggi teaches a method of decreasing Lipoprotein (a) by administering Tibolone to a human subject and that Lp (a) is a strong risk factor for coronary heart disease. The Examiner admits that Haenggi does not teach a method of employing Tibolone for inhibiting atherosclerosis.

The Examiner further asserts that Berglund teaches that Lp (a) has been implicated with an increased risk of atherosclerosis.

The Examiner concludes that it would have been obvious to one of ordinary skill in the art to employ Tibolone in a method of inhibiting

atherosclerosis. Applicants respectfully request reconsideration in light of Applicants' invention and the cited art.

Further, even considering Applicants' invention and the cited art, the differences between the prior art and Applicants' invention are many. To begin, apparently, the Examiner has understood that the present invention would relate to the effect of Tibolone on the levels of Lipoprotein (a) (Lp(a)), which is a factor that relates to a risk of atherosclerosis and coronary heart disease. However, in contrast, embodiments of the present invention have an atheroprotective effect that is due to direct effects on the vessel wall and is independent from an effect on Lp(a).

In the description, starting on line 29 of page 2 to page 3, line 24, it is explained that Tibolone has been subject to studies concerning the long-term effects on lipid metabolism of the compound, since the compound (in addition to estrogenic activity) also has progestogenic and androgenic properties. The latter properties are associated with negative effects on lipoproteins (see *e.g.* Haenggi p. 648, first part of left column). The studies indicated that the benificial decreasing effect of Tibolone on Lp(a), however, might be sufficient to counterbalance the negative effects of the compound on the other plasma lipoproteins (see description page 3, lines 9-15 and *e.g.* Haenggi, abstract, last sentences). Thus, Haenggi only teaches a potential balancing effect of Tibolone treatment on the plasma lipoproteins, but Haenggi certainly does not teach highly favorable effects of Tibolone on

Lp(a), which would motivate a person skilled in the art to use Tibolone for its atheroprotective effect.

Always a counter consideration for an obvious analysis, should be the secondary considerations, or objective indicia of non-obviousness. Here, Applicants invention produces both unexpected results and teaches against the art, thereby providing strong evidence of non-obviousness. For example, in hormone replacement therapy, estrogen is considered more favorable than the use of Tibolone (with its mixed estrogenic / progestogenic / androgenic profile) since Tibolone is expected to afford less protection against coronary artery disease (see Riggs, B.L., J. Clin. Endocrinology and Metabolism (1996), 81, p.2418, left column)(a copy of which is included for the Examiner's convenience). Accordingly, the artfield teaches away from Applicants' invention and one of ordinary skill in the art would not expect Tibolone to have such an atheroprotective effect.

Moreover, the atheroprotective effect of Tibolone is unexpectedly strong and completely independent from its effects on plasma lipoproteins or Lp(a). In the rabbit model used to demonstrate this effect Lp(a) does not play a role, since Lp(a) is absent in rabbit plasma. Accordingly, these are unexpected results.

The experiments illustrate that Tibolone, in comparison with estradiol in the cholesterol rabbit model, (in doses clinically equivalent to the estradiol doses used) has atheroprotective effects that are unexpectedly significantly

more pronounced than those of estradiol. For example (see example 2, Table III), Tibolone completely prevented cholesterol accumulation in the aortic arch, whereas estradiol did not lead to a reduction in cholesterol accumulation. Furthermore, fatty streak formation in the aortic arch was almost completely prevented by Tibolone treatment, whereas estradiol had only minor effects.

Therefore, in an embodiment, the present invention relates to the unexpectedly strong atheroprotective effects of Tibolone. Accordingly, Applicants respectfully request reconsideration of the rejection.

VI. CONCLUSION AND REQUEST

In light of this response, Applicants respectfully contend that the present invention is not obvious. Further, Applicants respectfully request that the Examiner contact Applicants' undersigned attorney to further the prosecution of the case. Please charge any required fees and credit any credits to deposit account 02-2334.

Sincerely,

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occurred in only a minority. For the women receiving tibolone there were incidences of 15% for vaginal bleeding and 18% for breast tenderness, which are similar to those reported in other studies (7). Significant problems with androgenicity did not occur. Finally, using state-of-the-art biochemical markers, the authors clearly demonstrated that tibolone therapy decreased bone turnover in a manner similar to estrogen therapy and found no indication that the androgen-like component resulted in a relative or absolute stimulation of bone formation.

Tibolone has not as yet been approved by the United States Food and Drug Administration. However, if the favorable results obtained with this study are confirmed by others, it seems likely that it will be. If this occurs, what should the role of tibolone be with respect to other available therapeutic options? Tibolone appears to be similar to estrogen in its effects on bone but has a somewhat different profile of extraskeletal effects. Its main advantage over cyclic therapy with estrogen and progestin appears to be the lower incidence of vaginal bleeding and breast tenderness. However, the low incidence of these symptoms with tibolone therapy does not appear to be very different from that achieved with so-called combined continuous hormonal therapy, in which a standard dose of estrogen and a low dose of progestin are administered without interruption. Whether long-term tibolone therapy will be associated with an increased incidence of breast cancer, as has been reported after ERT (8) in some, but not other, studies is unclear, and this issue is not likely to be resolved in the near future because of the large sample size that is required to obtain adequate statistical power.

The major disadvantage of tibolone therapy compared with ERT is its less favorable effect on the serum lipid profile. The beneficial effect of ERT on the serum lipid profile accounts, at least in part, for its protective effect against cardiovascular disease. Although the authors apparently measured serum lipids in the course of the clinical trial, they were not reported except as a footnote stating that serum HDL cholesterol was reduced by 30% in the treatment groups. Presumably, a subsequent paper dealing with this issue will be published elsewhere. Based on previous reports, however, long-term tibolone therapy (9) is not associated with a decrease in LDL cholesterol as occurs with ERT, and it maintains or reduces the pretreatment levels of HDL cholesterol, whereas oral ERT increases it (4). Like estrogen, however, it does reduce the serum concentration of lipoprotein (a), an independent risk factor for coronary artery disease (10). All-in-all, however, tibolone would be expected to afford less protection against coronary artery disease than does ERT.

If tibolone eventually is approved for use in the United States, it likely will be targeted to a relatively small proportion of postmenopausal women. It would have its greatest utility in treatment of early postmenopausal women who are experiencing hot flushes and other menopausal symptoms and who wish to be relieved of them, protected against postmenopausal bone loss, and have as few episodes of vaginal bleeding as possible. However, continuous combined estrogen-progestin therapy may accomplish the same goals with a more favorable effect of serum lipids. Moreover, for the late postmenopausal women of the type reported in the present article, hot flushes and related menopausal symptoms occur rarely. Thus, when drug intervention is needed in older postmenopausal women because of low bone mass, many would choose nonhormonal therapy such as nasal spray calcitonin or alendronate, antiosteoporotic compounds that have recently been approved by the United States Food and Drug Administration.

For many years, ERT has been the only practical choice of drug intervention in postmenopausal women to prevent osteoporosis. This situation now is changing dramatically, and American physicians soon will be in the favorable position of having multiple antiosteoporotic drugs to choose from. Tibolone would be a welcome addition to the clinician's therapeutic armamentarium, even though it may have limited and restricted usage.

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